

APPENDIX A

61. An LHRH antagonist comprising a peptide compound, wherein a residue of the peptide compound corresponding to the amino acid at position 6 of natural mammalian LHRH is selected from the group consisting of D-asparagine, D-threonine and D-glutamine, wherein the peptide compound has LHRH antagonist activity, inhibits ovulation in at least 50% of treated rats in a standard rat antioviulatory assay at a dose of 5 $\mu\text{g}/\text{rat}$, and has an ED_{50} for histamine release of at least 3 $\mu\text{g}/\text{ml}$, or a pharmaceutically acceptable salt thereof.
62. The LHRH antagonist of claim 61, which inhibits ovulation in at least 50% of treated rats in a standard rat antioviulatory assay at a dose of 2 $\mu\text{g}/\text{rat}$.
63. The LHRH antagonist of claim 61, which inhibits ovulation in at least 50% of treated rats in a standard rat antioviulatory assay at a dose of 1 $\mu\text{g}/\text{rat}$.
64. The LHRH antagonist of claim 61, which has an ED_{50} for histamine release of at least 5 $\mu\text{g}/\text{ml}$.
65. The LHRH antagonist of claim 61, which has an ED_{50} for histamine release of at least 10 $\mu\text{g}/\text{ml}$.
66. The LHRH antagonist of claim 61, which is about 8 to about 12 residues in length.
67. The LHRH antagonist of claim 61, which is 9 to 11 residues in length.
68. The LHRH antagonist of claim 61, which is 10 residues in length.
70. The LHRH antagonist of claim 61, wherein the residue corresponding to the amino acid at position 6 of natural mammalian LHRH is D-asparagine.
71. A peptide compound comprising a structure:

A-B-C-D-E-F-G-H-I-J

wherein

A is pyro-Glu, Ac-D-Nal, Ac-D-Qal, Ac-Sar, or Ac-D-Pal;

B is His or 4-Cl-D-Phe;

C is Trp, D-Pal, D-Nal, L-Nal-D-Pal(N-O), or D-Trp;

D is Ser;

E is N-Me-Ala, Tyr, N-Me-Tyr, Ser, Lys(iPr), 4-Cl-Phe, His, Asn, Met, Ala, Arg

or Ile;

F is selected from the group consisting of D-Asn, D-Gln and D-Thr;

G is Leu or Trp;

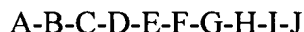
H is Lys(iPr), Gln, Met, or Arg;

I is Pro; and

J is Gly-NH₂ or D-Ala-NH₂;

or a pharmaceutically acceptable salt thereof.

73. A peptide compound comprising a structure:



wherein

A is pyro-Glu, Ac-D-Nal, Ac-D-Qal, Ac-Sar, or Ac-D-Pal;

B is His or 4-Cl-D-Phe;

C is Trp, D-Pal, D-Nal, L-Nal-D-Pal(N-O), or D-Trp;

D is Ser;

E is N-Me-Ala, Tyr, N-Me-Tyr, Ser, Lys(iPr), 4-Cl-Phe, His, Asn, Met, Ala, Arg

or Ile;

F is D-Asn;

G is Leu or Trp;

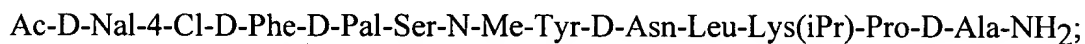
H is Lys(iPr), Gln, Met, or Arg;

I is Pro; and

J is Gly-NH₂ or D-Ala-NH₂;

or a pharmaceutically acceptable salt thereof.

74. A peptide compound comprising a structure:



or a pharmaceutically acceptable salt thereof.

75. A peptide compound comprising a structure:

Ac-D-Nal-4-Cl-D-Phe-D-Pal-Ser-Tyr-D-Asn-Leu-Lys(iPr)-Pro-D-Ala-NH₂;
or a pharmaceutically acceptable salt thereof.

76. A pharmaceutical composition comprising the peptide compound of any one of claims 61-68, 70, 71 or 73-75, and a pharmaceutically acceptable carrier.

77. A packaged formulation for treating a subject for a disorder associated with LHRH activity, comprising the peptide compound of any one of claims 61-68, 70, 71 or 73-75, packaged with instructions for using the peptide compound for treating a subject having a disorder associated with LHRH activity.